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- **FOXO transcription factors**
  Mechanisms and pathways

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Success is where preparation and opportunity meet

If someone asks you about the meaning of the word 'success', what would your answer be? Some people may defi ne it as "making more money", others may say success signifies "achievement of goals", and most interestingly "making others jealous" can be a valid answer.

The general definition of the word success is usually used to describe a completion of an intended task or job. For our team, it means IBScientific! Michael Angier, founder and CIO of Success Networks International, says "Success is the result of steadily taking action on our most important goals.

When we consistently focus our energies and our efforts upon what matters most, we can't help but be successful". It is almost two years now since the candle of IBScientific was lighted. Since then, the light has got brighter and brighter after every success. IBScientific Magazine, soon followed by IBS Journal of Science, IBSAC2006 and, in the near future, the IBScientific and FOREM conference in Algiers from 16 to18 April 2007, are all measures of how successful the initiative is. Michael Angier's description is fully applicable to IBScientifi c, where we keep preparing actions and taking opportunities to reach our untimate goal. Th e light of IBScientific, now, has reached the five continents, and attracted different nationalities and has been praised by seniors and VIPs.

We think that there is no real motivator to more success like success itself. This time, the ambition got bigger and the light is even brighter; beside its other activities, IBScientific, in conjunction with FOREM, is organising its largest event to date, a three-day conference in Algiers next April. The conference aims at setting up a meeting point where Algerian competences inside Algeria and abroad get together, for the first time, to discuss possible directions towards the country's economy development. This is a very important event, as it can be a start of a strong collaborative network. The conference is expected to be a platform for knowledge exchange followed up by course of actions. It is therefore an opportunity to anyone who wants his/her voice and opinion to be heard. This event may well be an excellent prototype and example for other developing nations.

I trust you agree that IBScientific has been a success, and this only motivates to put more efforts into other activities. We want to give the candle an ever lasting light and this can not happen without the contributions of our readers and members, so help us make its light brighter with more success.?

Elhadj BENLHELIFA
IBScientific Advertisement Manager

SiGe: Virtual or Reality?

Preview by: **Abdeldjalil BENNECER**

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Semiconductor materials with high mobility, high saturation velocity or high bandgap hold great promise for complementary metal oxide semiconductor (CMOS) technology and optoelectronics applications. A number of III-V materials like GaAs, InP with the above properties already dominate a few small market niches such as radio frequency (RF) power amplifiers. Furthermore, having a direct bandgap and owing to the flexibility offered in engineering their energy levels, they are able to generate light amplification (lasing action), and so they are ideal for optoelectronics devices. Silicon remains the main element used in the mainstream integrated circuit microelectronics because of the mature and low-cost fabrication processes, despite its inferior electronic properties compared to III-V compounds. As an alternative, Silicon germanium (SiGe) grown on a silicon wafer has gained considerable interest in order to improve silicon properties and retain the advantages offered by its [Silicon] current technology. In order to realise the full potential of Si/SiGe heterostructures, more sophisticated techniques for their growth, band structure and strain engineering are required. In this issue, Rihani [1] reviews SiGe material properties, including the band structure engineering and the growth techniques leading to an important improvement on growth technique to add to our capabilities.

This work builds on exciting developments in the field of virtual substrates. These are completely miscible materials in Si like Ge to be graded slowly from zero (pure Si) to around 30% over a few microns resulting in relaxed alloy of SiGe buffer layer. Then, when a thin layer of strained Si is grown on SiGe substrate, it results in higher mobility of carriers. The mobility of carriers, μ, is a measure of the proportionality factor of the speed of carriers in the material in the presence of an applied electric field. Specifically, the carriers are able to move faster; which in turn means that transistors can switch at higher frequencies.

In 1955, Glickman published the first paper on the magnetoresistance of silicon germanium alloy [2]; but the first SiGe devices were in the original patent for the bipolar transistor where the idea and the physics description of SiGe base heterojunction bipolar transistor (HBT) were discussed in [3]. Yet it was not until 1975, when Kasper *et al.* [4] at AEG Research Centre (now Daimler Chrysler) in Ulm, Germany succeeded to demonstrate the epitaxial growth of SiGe heterostructures using molecular beam epitaxy (MBE) required by such a transistor. Whereas, the 1980s research focus was on developing growth technology, the 1990s was dominated by the development of HBT and the 2000s by strained Si.

Engineering virtual substrates with improved electronic properties was easy: this makes use of conventional growth techniques such as Molecular Beam Epitaxy (MBE) and Chemical Vapour Deposition (CVD). The more difficult task was to reduce the dislocations density in the epitaxial layer. The threading dislocations are undesirable in material growth because they tend to propagate in the upper device layers and hinder its performance. For instance, in optoelectronic components, dislocations may contribute to the electron hole non-radiative recombination process, thereby reducing the quantum efficiency of those devices.

HBT is the most mature of the SiGe devices whereas the author [1] concentrates more on the material and strain properties together with strain relaxation techniques useful for CMOS, RF applications and III-V materials integration. Then, the electronic properties and band structure are outlined for perhaps potential

future optoelectronic devices previously dominated by higher cost III-V materials. In the conclusion, the author improves on a simple and elegant growth technique known as terrace grading. He emphasises that the relaxation of the first terrace is critical and can help reduce the threading dislocation density in all subsequent layers. The author's guidelines are promising.

Naturally, challenges remain and claims to dethrone the silicon as the dominant mainstream microelectronics technology have not yet been successful. Growing defect-free SiGe epitaxial layers is still unresolved. Also, SiGe is a poor thermal conductor so a transistor operating on thick virtual substrates will cancel the advantages of strained Si. Currently, attention is focusing on finding a much thinner virtual substrate design with acceptable properties. The author points out these difficulties and specifies the parameters to be addressed in order to optimise the relaxed SiGe for particular applications.

Whatever the next stage of development might be, the review by Rihani covers a new and promising set of possibilities for the semiconductor roadmap, with all the potential that it holds.

1. **S. Rihani, IBScientific Journal of Science, vol. 2(1), pp. 18-23, 2007.**
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FOXO transcription factors: Mechanisms and pathways

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Abstract

Transcription factors are key regulators of cellular pathways, and instrumental in directing the activity of the transcriptional machinery. Forkhead transcription factors are winged helix transcription factors that regulate a multitude of processes ranging from early embryonic development to ageing. Recent work has identified Forkhead box O (FOXO) factors as mediators of signals emanating from the PI3K/PKB pathway. In the review, an overview of the regulation, activity and function of these transcription factors is highlighted.

1. Forkhead Transcription Factors

Forkhead transcription factors are a large family of proteins, consisting of at least 40 members in humans [15]. They are characterised by monomeric DNA binding domain with a butterfly-shaped structure of 110 amino acids called the winged helix motif or the forkhead box (Fox) [85, 99]. They were first discovered as important regulators of development with an essential role in organogenesis [55]. Most of the Fox members are believed to bind DNA as monomers with the exception of FOXP family of proteins [97]. This family of proteins are important for stem cell self-renewal and commitment, cell cycle regulation, survival, metabolism, DNA repair, oxidative stress, differentiation, cytoskeleton dynamics, immuno-modulation, and cell activation [55].

2. FOXO Transcription Factors

The FOXO transcription factors are the mammalian homologues of DAF-16 in C. elegans [51]. DAF-16 has been linked to regulation of ageing on the nematode worm, and was implicated in insulin signalling downstream of the conserved age-1/akt (PI3K/PKB) pathway [51]. FOXO transcription factors contain a unique five amino acid (GDSNS) insertion immediately prior to helix H3 within the forkhead domain that is absent in all other FOX transcription factors [4]. In humans and other mammals four members of this family have been characterised FOXO1 (FKHR), FOXO3a (FKHRL-1), FOXO4 (AFX) and FOXO6 [4].

Structure of FOXO transcription factors

All Forkhead transcription factors, including the FOXO family members, are characterised by a Forkhead domain (FHD, the DNA binding domain) flanked by C- and N-termini that have been shown to

act as trans-activation domains [100] (Figure 1a). The FHD domain contain helix-turn-helix domain, making the forkhead transcription factors members of the winged-helix domain transcription factors [100]. The FHD domain is composed of three α-helices and three β-sheets and two loops or wings; the wings, in particular, are particularly important for DNA binding [54]. At the C-terminal of the FHD domain, a non-classical bipartite nuclear localisation signal (NLS) followed by three arginine residues specifically characterise the FOXO transcription factors. Within this NLS, a PKB phsosphoryaltion motif (RXRXXS where the S residue is phosphorylated) is responsible for FOXO nucleo-cytoplasmic shuttling [101]. The NLS is also important for the binding of 14-3-3 molecular chaperone leading to cytoplasmic relocalisation [92]. Some other proteins bind the FHD leading to gene expression attenuation probably through the inhibition of 14-3-3 binding such as FOXG1, SMAD3/4, SIRT1, p53, p300, CBP and SIRT1 [32] (Figure 1b).

The N-terminal trans-activation domain contains a proline-rich domain that is important for protein-protein interaction with transcriptional co-factors such as PGC1α, and p300/CBP [32]. The binding of p300 to the N-terminal is implicated in directly inhibiting 14-3-3 binding to a second NLS site at the N-terminus of this domain [62]. This NLS site, much like the NLS embedded in the FHD domain, harbours a PKB consensus phosphorylation site that is important for cytoplasmic delocalisation of the FOXO transcription factors [62]. The C-terminal domain, on the other hand, contain one nuclear export signal (NES), that plays a role in binding Ran, a small GTPase of the RAS family that was shown to be important for nuclear-pore complex, leading to nuclear export of FOXO transcription factors [81]. Ran GTPase also binds CRM1 (Chromosomal region maintenance protein 1) leading to translocation of proteins to the cytoplasm [53]. Interestingly, both proteins have been shown to interact with NES at the C-terminal trans-activation domain leading to the cytoplasmic import of FOXO transcripticon factors in an 14-3-3 dependent mechanism [92]. The function of NES within the C-terminal has been shown to be partially dependent on phosphorylation of the nearby serine and threonine residues by PKB [81, 104]. At the C-terminus of this trans-activation domain, an LXXLL motif has been shown recently to specifically mediate SIRT1 binding to FOXO transcriptiona factors (FOXO1, FOXO4 and FOXO3a) [68] (Figure 1b). Notably, β-catenin also binds at the same region and attenuates FOXO dependent transcriptional regulation, however, the exact role of LXXLL motif in this interaction is yet to be investigated [23]. FOXO transcription factors also have features that are unique to each FOXO family member. FOXO6, for example, is characterised by a short C-terminus that lacks phosphorylation sites adjacent to the NES leading to its constitutive nuclear localisation [43]. FOXO3a, on the other hand, contains two NES sites at the C-terminus are essential for its nuclear exclusion [12].

Physiological roles of FOXO transcription factors

FOXO transcription factors are involved in the regulation of normal homeostasis and neoplasia. Therefore, a brief outline of their role in cancers will be briefly mentioned followed by gene targeting studies.

FOXO transcription factors in human neoplasia

FOXOs were first found in translocation mutations in acute lymphoblastic leukaemia (MLL-FOXO4/, MLL-FOXO3a) and alveolar rhabdomyosarcoma (PAX3 or PAX7-FOXO1) [32, 84]. This is consistent with their roles both in haematopoiesis (FOXO4 and FOXO3a) and muscle development (FOXO1), [32]. Trans-activation domain of FOXOs in the fusion chimeras have been shown to be essential for transformation in these malignancies, by acting in a dominant-negative fashion to inhibit the activity of wild-type FOXOs in the induction of apoptosis [2, 5, 8, 22]. Interestingly, the loss of non-translocated FOXO allele (wild-type) in rhabdomyosarcomas is important for the development of tumours in mice models [45], suggesting a possible tumour suppression activity.

FOXO1

Foxo1 is ubiquitously expressed but highly abundant in adipocytes and muscle cells [28]. The foxo1 homozygous knockout mice are embryonic lethal with vascular defects [27]. FoxO1 seems to be an essential regulator of embryonic vessel formation, affecting both vasculargenesis and angiogenesis through the regulation of endothelial cell differentiation, proliferation and survival [78, 79]. FOXO1 is also implicated in the differentiation of myoblasts [38], and more recently pancreatic β-cell normal development, differentiation and response to insulin [48, 67, 73]. Although most of the targets involved in these pathways remain to be validated, some new targets have been characterised such as ANG1, ANG2, eNOS, G6P, PDX1, NEUROD, MAFA and adiponectin. Angiopoietin 1 and 2 (ANG1, ANG2), which modulate endothelial function and angiogenesis [20, 79]. Nitric oxide synthase 3 gene (eNOS) is important for vessel formation and maturation [79]. Glucose-6-phosphatase gene (G6P) regulates insulin signalling in liver and muscles [69], PDX1 links insulin signalling to β-cell function [47], NEUROD and MAFA protects β-cell from failure [48], and adiponectin is involved in adipose tissue homeostasis and ageing [90].

FOXO4

The foxo4-/- mice were indistinguishable from their wild-type littermates, most likely due to compensation by foxo1 and foxo3a [37]. This is corroborated by the fact that FOXO3a and FOXO1 target the same genes as FOXO4 [32]. This is also confirmed by the low expression of FoxO4 mRNA in most tissues with the exception of endothelial cells [26, 37]. Consistently, FOXO4 is the predominant factor that regulates endothelial progenitor cells survival through the activation of BIM expression [91].

Interestingly, FOXO1 regulates endothelial cell development and survival [37], and BIM expression was induced in endothelial progenitor cells by FOXO3a and FOXO1 leading to apoptosis [79].

FOXO3a

foxo3a is ubiquitously expressed, with high expression in brain and ovarian tissues [28]. FOXO3a is the main FOXO isoform expressed in haematopoietic cells [17, 59]. foxo3a homozygous knockout mice did not show any overt phenotypic distinctions from their wild-type littermates in the initial studies, but further studies have demonstrated a role in ovary and haematopoietic development [16, 37]. foxo3a-/- mice show an abnormal development of ovaries and sterility in both sexes [16]. This is achieved through the deregulation of ovar-

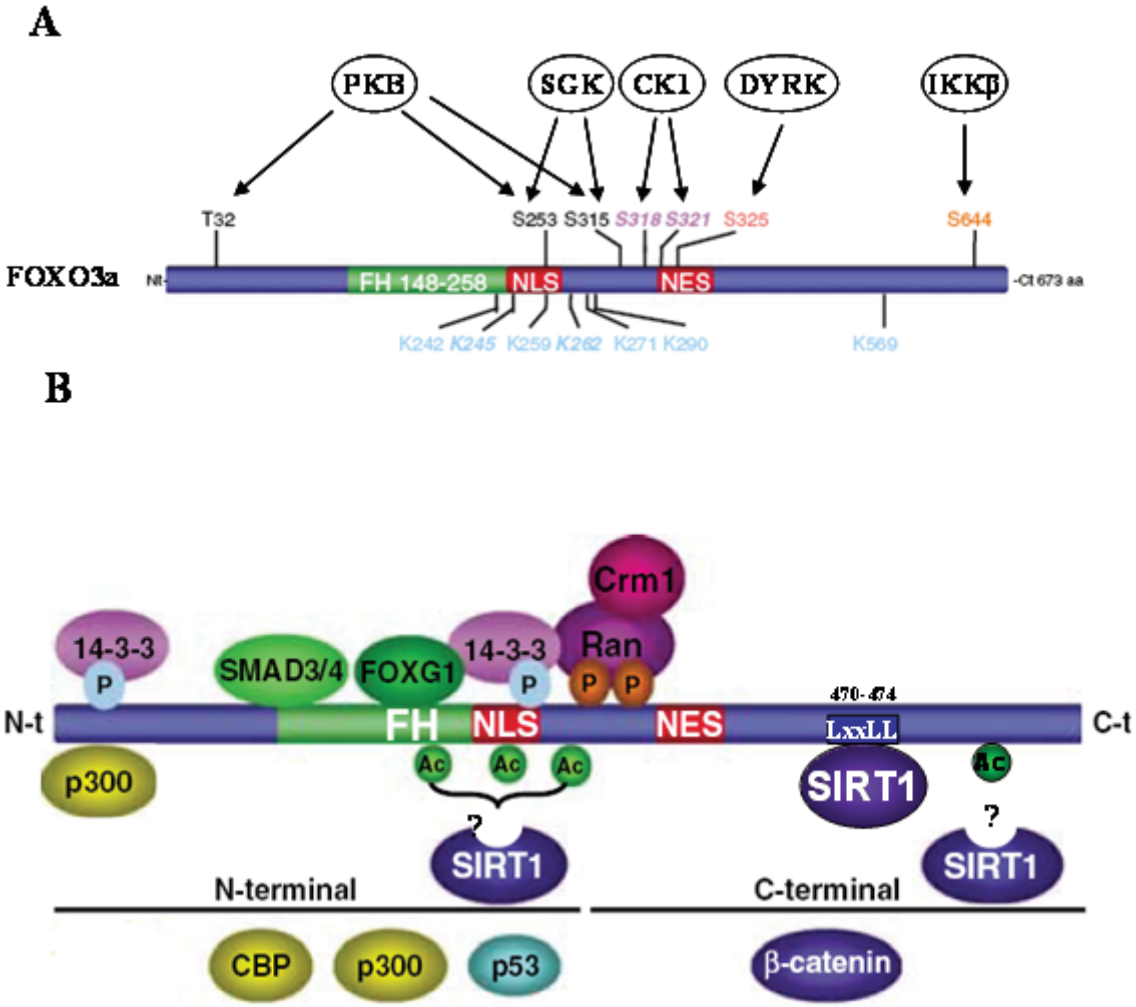

Figure 1: FOXO3a structure and regulation

A. FOXO3a share high homology with other FOXO transcription factors. They all contain forkhead domain (FHD), NLS and NES. They also share conserved post-translational modification sites. FOXO3a contain a unique IKK site at S644 residue. The lysine (K) residues represent potential acetylation sites.

B. FOXO3a have been shown to bind different proteins that regulates its nuclear cytoplasmic shuttling (14-3-3, Ran and Crm1), attenuates its transcriptional activate (-catenin, p300 and SIRT1). It has also been shown to bind different transcription factors (SMAD3/4, FOXG1, p53).

The figure is modified from [32]

ian follicular development owing to accelerated differentiation [16]. FoxO3a functions by maintaining the developmental arrest state of primordial follicles, and can not be compensated by other FOXO factors [37]. FOXO3a has been shown to maintain cells in a quiescent (arrest state) as a protection against damaging insults through the modulation of different target genes such as p27Kip1, and superoxide dismutase 2 (SOD2 or MnSOD) [37, 52, 64]. Moreover, Castrillon *et al.* (2003) have reported some haematological malignancies associated with foxo3a disruption [16]. foxo3a-/- mice showed mild compensated anaemia with reticulocytosis in the early weeks of birth [16], and after 8 months develop lymphoproliferative disease with multi-organ infiltrates, and multi-system inflammation [59]. FOXO3a has also been shown to regulate inflammation in arthritis through modulating the expression of FASL in neutrophils [44]. Under inflammatory conditions, neutrophils from foxo3a-/- mice displayed high levels of apoptosis compared to their wild-type littermates [44]. FOXO3a has been implicated in both TGF-β and IL-1 signalling in human rheumatoid arthritis and its model in K/BxN mice [44]. Lin *et al.* have provided some evidence that FOXO3a regulates haematopoiesis, and in particular lymphocyte homeostasis by modulating NF-κB signalling, another TGF-B downstream target [59]. foxo3a$^{-/-}$ mice displayed T cells deficiency, hyperactivity, increased levels of FoxJ1 and elevated NF-κB activity, accompanied by decrease in its negative regulators IκBβ and IκBε [59]. The mechanism by which FoxO3a induces activation of NF-κB remains to be elucidated. Binding and sequestration of FoxJ1 by FoxO3a can be an attractive and feasible mechanism [59]. Notably, a previous study identified a similar process in neuronal cells involving FOXO3a and FOXG1 cooperation to modulate p21Cip1 expression downstream of TGF-β signalling [83]. FOXO3a is further implicated in haematopoiesis through work done on FOXO3a fusion proteins involved in acute leukaemia such as MLL (mixed lineage leukaemia gene)-FOXO3a [84]. In this, fusion protein FOXO3a is able to bind DNA and is usually truncated at the amino terminus [84], hence abro-

gating regulatory sites for PKB and p300 binding [93]. MLL-FOXO3a induces specific myeloid and sometimes lymphoid expansion of progenitor cells characteristic of the acute leukaemia [84]. It also promote self-renewal potential of progenitor cells [84]. These results together suggest that FOXO3a is involved in the regulation of homeostasis, development, proliferation, and survival of progenitor as well as committed haematopoietic cells, making it a prime candidate for regulating cell death, cell cycle arrest and differentiation of CML cells and BCR-ABL+ cell lines. Already, some reports have suggested its role in as a downstream target of STI571 to induce cell cycle arrest through modulation of p27Kip1 [49].

Regulation of FOXO activity

The FOXO transcription factors are generally regulated in a similar fashion, the next section will focus on the regulation of FOXO3a. First, I will brifely mention C.elegans daf16 regulation as it shares high homology with FOXO3a protein. I will then focus on FOXO3a regulation.

Regulation of daf16 activity

DAF16 of Caenorhabditis elegans is implicated in insulin signalling and the regulation of ageing [58, 72]. DAF16 is a downstream target of insulin/insulin like growth factor (IGF) signalling involved in the regulation of calorie restriction and metabolism, a function that is conserved in higher eukaryotes [46]. In an allele dependent manner, disruption of daf-2, age-1, or akt-1/2 the C.elegans orthologues of the mammalian IGF receptor, PI3K and PKB respectively, resulted in the dauer phenotype and extended life spans [58, 72]. Disruption of daf16, on the other hand, results a shortened life span and inhibition of the dauer formation, suggesting that DAF16 is downstream target of the AGE1/AKT1/2 pathway [58, 72]. DAF16 activity was later shown to be negatively regulated by akt1/2 leading to its phosphorylation, inactivation and cytoplasmic localisation [74]. Similar pathways were later unearthed in Drosophila linking hormonal regulation to ageing through the PI3K-PKB-FOXO pathway [29, 41]. Other members of this pathway have also been found to regulate longevity, DAF18 (PTEN homologue in C.elegans) that inhibits PIP production and is necessary for PKB1/2 activation, and sir2 deacetylase (SIRT1 homologue) also negatively regulates ageing through modulation of daf16 transcriptional activity [34].

Regulation of FOXO3a activity

FOXO3a is implicated in the regulation proliferation, apoptosis, differentiation, oxidative stress, DNA damage, metabolism and senescence [1, 3]. These processes are important for cancer biology rendering FOXO3a an attractive target for therapy. Most of the work has concentrated on understanding the regulation of this protein and the identification of its target genes. FOXO3a is regulated by phosphorylation, acetylation and degradation affecting its ability to modulate target gene expression. A brief outline of these regulatory mechanisms will be discussed.

Phosphorylation

Phosphorylation plays a major role in the cellular localisation and activation of FOXO transcription factors, and is mainly mediated by PKB (Figure 1a). PKB phosphorylates FOXO3a leading to its inactivation, cytoplasmic relocalisation and nuclear export [50]. Under insulin/serum starvation conditions, PKB is dephosphorylated and inactived due to the low PIP3 levels, and FOXO3a localises to the nucleus, but after stimulation and/or activation of PKB, FOXO3a relocalises to the cytoplasm [6, 11, 22, 35, 50, 70, 88]. Expression of constitutively active myristilated PKB (myr-PKB), for example, in serum starved cells leads to constitutive cytoplasmic localisation of FOXO3a [11]. FOXO3a transcription factor, like DAF16 in C.elegans, and dFOXO in D.melanogaster, is negatively regulated by PKB through phosphorylation at the consensus site RXRXXS/T [101]. Three of the four sites phosphorylated by AKT1/2 in DAF16 are conserved in FOXO3a and corresponds to T32, S253 and S315 [101] (Figure 1a). S253 is located in FHD within the nuclear localisation signal, and was shown to be specifically and exclusively phosphorylated by PKB [13]. The mutation of this serine to a neutral residue, such as alanine inhibited further phosphorylation of FOXO3a in other regions of the proteins by PKB or other kinases [13]. This suggest that this site is necessary to prime other sites for phosphprylation [101]. The FOXO3aS253A mutant is constitutively nuclear under different conditions including myr-PKB activation [13]. Therefore, the S253 is called the "gatekeeper site" [101]. This site is believed to inhibit DNA binding, negatively charging the NLS and changing its conformation [12]. It is also implicated in inhibition of nuclear re-import [12]. The conformational change caused by S253 phophorylation exposes other sites on the N- and C-termini, leading to phosphorylation of T32, and S315, respectively [32] (Figure 1a). The T32 residue is preferentially phosphorylated by PKB, but can also be modified by serum/glucocorticoid regulated kinase (SGK) in vitro [13]. This phosphorylation seems to be mediated by PKB in vivo as specific inhibition of PKB but not SGK abrogates T32 phosphorylation [13]. T32 phosphorylation has also been shown to inhibit p300 binding to FOXO3a N-terminus resulting in 14-3-3 chaperone binding and recruitment of RanGTPase and CRM1 proteins to transport FOXO3a to the cytoplasm [62] (Figure 1b). The third PKB site, S315, resides adjacent to the NES at the C-terminus and its phosphorylation leads to conformational changes that facilitate direct 14-3-3 binding and activation of the RanGTPase and CRM1 complex [12]. Although this phosphorylation is mediated by PKB or SGK activity in vitro, the in vivo evidence support SGK as the primary kinase to phosphorylate this site, nonetheless, PKB can substituted for in in the absence of SGK [13]. These three sites of phosphorylation are responsible for FOXO3a cytoplasmic localisation where it binds 14-3-3 and are stabilised at the cytoplasm till conditions arise which allow their dephosphorylation. The phosphoatase involved in the dephosphorylation of these three sites is yet to be investigated, but recent evidence from C.elegans support a role for enhancers of the akt-1 (eak) phosphotases in dephosphorylating daf16 [40]. Mutation of three sites to alanine, and generation of FOXO3aAAA or FOXO3a(A3), leads to constitutive nuclear localisation [13, 101]. This however inhibits any further phosphorylation of the protein by other kinases [80, 81, 102].

Studies of the speed and rate of nuclear-cytoplasmic shuttling of FOXO3a revealed the presence of other regulatory sites that accelerate nuclear export [13], however, most of our understanding of non-PKB phosphorylation sites was accomplished using FOXO1 [101]. CK-1 (casein kinase-1) has been implicated in the phosphorylation of two sites adjacent to the S319 in FOXO1, S322 and S325, that correspond to S318 and S321 in FOXO3a, respectively [81]

(Figure 1a). These two sites are dependent on S315 phosphorylation and are important for nuclear–cytoplasmic shuttling [81]. The site at position in S329 in FOXO1 corresponding to S324 in FOXO3a is phosphorylated by DYRK1a (dual-specificity tyrosine "Y" phosphorylated and regulated protein kinase family 1a) proteins, and seem to be constitutively phosphorylated in vivo independent of PKB or CK-1 activity [102]. This stretch of phosphoserine (S315, S318, S321, S324) act as an acidic patch that facilitates the binding to Ran GTpase and CRM1 and hence accelerating the nuclear export of FOXO3a [92]. Interstingly, FOXO6 lacks this region containing the serine patch and is constitutively nuclear. The reintroduction of FOXO3a sequences into FOXO6 reading frame resulted in growth factor-dependent nuclear-cytoplasmic shuttling dynamics [43].

FOXO3a localisation is correlated and affected by PKB activation in breast cancer patients' samples. It also correlated with the activity of IκKβ in both normal and tumour samples [39]. Using FOXO3a(3A) mutant, Hu *et al.* (2004) reported nuclear exclusion of FOXO3a in the presence of IκKβ but not IκKα [39]. In this study, IκKβ has been shown to bind and phosphorylate FOXO3a at S644 residue that is not conserved in other FOXO transcription factors [39] (Figure 1a). This phosphorylation leads to cytoplasmic retention of FOXO3a, poly-ubiquitination and degradation [39]. This unique mode of regulation is independent of other phosphorylations, and expression of FOXO3a overrides proliferation and tumourgenesis of IκKβ signalling [39]. This phosphorylation has as yet to be validated in other tumour cells.

Recent work identified a PKB independent mechanism regulating FOXO3a nuclear localisation [56]. The mammalian Ste20-like kinases (MSTs) bind and phosphorylated FOXO3a at S207 leading to disruption of 14-3-3 binding followed by its nuclear localisation under stress conditions (hydrogen peroxide treatment) [56]. This interaction is conserved among other FOXO transcription factors including daf16 [56].

Reversible acetylation of FOXO3a

FOXO3a phosphorylation is important for its nuclear-cytoplasmic shuttling, and other post-translational modifications are necessary to fine-tune its transcriptional activity. Reversible acetylation is a post-translational modification mediated by transferring an acetyl group to lysine residues in proteins [18]. It was first discovered in histone tails, whereby acetylation leads to opening of chromatin and activation of transcription [18]. Deacetylation, on the other hand, induces closed chromatin structure and repression of gene expression [18]. Protein acetylation is mediated by different histone acetyltransferases (HATs) that have different specificities and target consensus sites [33]. Calcium responsive element-binding (CREB)-binding protein (CBP/p300) and p300/CBP-associated factor (PCAF) are the main acetyltransferases involved in regulation of histone and transcription factors acetylation [33]. Their activity is reversed by histone deacetylases (HDACs), which remove the acetyl group from lysine residues. Due to the fact that they were first discovered to deacetylate histones, they still retain the HDAC acronym, although they have other proteins as substrates and in particular transcription factors [21]. HDACs are divided into three classes, HDAC class 1 are of low molecular weight 22-55kDa, share homology in their catalytic domain, and related to RPD3 deacetylase in yeast [21]. Class I includes HDAC 1, 2, 3, and 8. Class II includes HDAC 4, 5, 6, 7, 9 and 10 are of high molecular weight and show high homology to HAD1 yeast deacetylase [21]. There is one HDAC (HDAC11) that share homology to both class I and II HDACs [21]. Class III of HDACs (SIRTs) does not have histones as their primary substrates and have an absolute requirement for NAD in vivo and in vitro [42]. They are also insensitive to classical HDAC class I and II inhibitors, such as Trichostatin A (TSA) [42]. SIRTs show high homology to Sirtuins in yeast, hence the name, and are involved in ageing, metabolism and transcriptional regulation [42]. They contain seven members in humans and mice (SIRT1 to SIRT7) that differ in target specificity but exhibit redundant activities in vitro [42] and are inhibited by Nictonimaide (Vitamin B3) [61].

FOXO3a acetylation

CBP and p300 complexes acetylate transcription factors in general to attenuate their transcriptional activity, and act as a co-factor to recruit the transcriptional machinery leading to chromatin remodelling. This was elegantly demonstrated in p53 dependent transcription [93]. CBP and p300 have recently been shown to bind and acetylate FOXO3a both in vitro and in vivo [14, 62, 66]. This interaction is totally dependent on PKB inactivation and seems to be prerequisite to acetylation [14, 66]. FOXO3a has previously been shown to bind p300/CBP at the N-terminus masking the first 52 amino acids at the N-terminus under serum starvation conditions but this interaction is disrupted by PKB dependent phosphorylation of T32, and binding of 14-3-3 after erythropoietin addition to erythroid progenitors [62]. Further studies showed that CBP/p300 binds the C-terminus and FHD domains of FOXO3a [14, 66] leading to acetylation at different lysine (K) residues : K242, K259, K271, K290, and K569 but not at the N-terminus [14]. The discrepancy between the two findings may be explained by cell type specific differences [14, 62, 66]. Furthermore, the in vitro studies showed binding under hydrogen peroxide treatment [14, 66]. Interestingly, binding of □-catenin at the C-terminus was specifically achieved under stress conditions [23]. They also can be reconciled with studies in C.elegans showing binding of CBP to both C and N-termini of DAF16, so that C-terminal of CBP binds the N-terminus of daf16 and vice versa [71]. The availability of two interaction domains in both CBP and FOXO3a may imply that two units of CBP bind FOXO3a, or more importantly, two FOXO3a proteins bind CBP at the different ends explaining the activation of genes with multiple Forkhead-binding sites [93]. Findings that stress induced binding of FOXO3a to CBP/p300 increases acetylation of FOXO3a [14, 66], may be partly explained by binding to more than one subunit of CBP/p300 . In vitro studies also revealed that pCAF can act as a HAT for FOXO3a [14, 66], but this is confounded by the fact that pCAF is usually associated with p300/CBP HATs.

FOXO3a deacetylation

Reversible acetylation is usually a transient modification, that is reversed by HDACs, and treatment of cells with HDAC inhibitors such as TSA or nicotinamide lead to accumulation of acetylated histones and transcription factors [7]. SIRTs proteins are implicated in different pathways including stress response, differentiation and longevity in conserved pathway from yeast to humans [7]. They have recently been shown to deacetylate p53, leading to gene expression attenuation [61, 96]. In 2004, several groups have identified SIRT1 as direct binding partner of FOXO transcription factors under stress

conditions [14, 19, 30, 57, 66, 95, 103]. This interaction is conserved also in C.elegans as Sir2 binds and deacetylates daf16 leading to differential gene expression, and longevity phenotype [98]. These results were inconsistent with each other at different levels, but showed in general that FOXOs bind SIRT1 under stress conditions and especially hydrogen peroxide (H2O2) induced stress [30] (Figure 1b). SIRT1 binding to FOXO3a leads to deacetylation of FOXO3a that is also facilitated by class I and II HDACs, leading to attenuation of gene expression [14, 66]. Upon oxidative stress, FOXO3a localises to the nucleus and is then acetylated, and further modifications are may be needed for it to bind SIRT1 [14, 66]. Notably, constitutively active FOXO3a(A3) fails to bind SIRT1 under any stress condition suggesting a need for further modifications, and paradoxically, SIRT1-FOXO3a interaction requires PKB phosphorylation of FOXO3a [14, 66]. FOXO3a is phosphorylated by PKB in the nucleus leading to its nuclear exclusion in optimal growth conditions, but PKB may act as a stress sensor facilitating FOXO3a binding to HATs and HDACs favouring gene activation of reactive oxygen species (ROS) scavengers genes such as catalase and SOD2 [52, 60, 89]. This may also be explained by the finding that JNK is involved in FOXO3a nuclear localisation in cooperation with PKB. Under drug induced ROS, JNK1/2 inhibition of FOXO3a reverses PKB-dependent localisation [87]. Work on FOXO4, however, has shown that JNK1/2-dependent phosphorylation at threonine 447 and threonine 451 led to nuclear localisation and transcriptional activation independent of PKB activity [24]. T447 and T451, however, are not conserved between FOXO3a and FOXO4 [101]. More studies are needed to explore the link between phosphorylation and reversible acetylation of FOXO3a and to elucidate the exact outcome of FOXO3a-SIRT1 interaction. So far, reports that investigated FOXO3a-SIRT1 interaction focused on the effect of deacetylation on FOXO3a dependent gene expression [14, 19, 30, 66].Brunet *et al.* (2004) demonstrated that FOXO3a acetylation increased in HEK293 cells in response to heat shock and hydrogen peroxide treatment, but not UV treatment [14]. Motta *et al.* (2004), on the hand, reported an increase in acetylation after all these environmental cues in HeLa cells [66]. This may be due to the fact that HeLa express low levels of p53, another stress-dependent binding partner of SIRT1, while HEK293 cells are wild-type to p53 expression [30]. Although this remains to be tested, it suggests a possible compensatory role for FOXO3a in the absence of p53 [30]. The FOXO3a-SIRT1 interaction leads to activation of p27Kip1 and other negative regulators of cell proliferation (e.g. GADD45), but repression of Bim and FasL gene expression, suggesting that SIRT1 binding to FOXO3a tip the balance towards cell survival [30]. The FOXO3a-SIRT1 is further complicated by the fact that p300 is a direct target of SIRT1 deacetylation leading to its sumolation and inhibition [9]. This possibly indicates that SIRT1 attenuates FOXO3a-mediated transcriptional regulation through both direct deacetylation and restraining further acetylation by p300 [93].

Ubiquitination of FOXO3a

In the cytoplasm, FOXO3a is subject to another layer of post-translational regulation leading to its degradation after growth factor stimulation [77]. Inhibition of PI3K sufficient to block this degradation, suggesting that this pathway is further implicated in the proteolysis of FOXO3a [77]. Addition of proteasome inhibitor MG132 resulted in the inhibition of PKB dependent degradation of FOXO3a, suggesting that the degradation is proteasomal [77]. Furthermore, PKB activation was required for FOXO3a poly-ubiquitination and degradation [77]. PKB therefore, seems to promote survival and proliferation through both cytoplasmic localisation and poly-ubiquitination of FOXO3a. Recently, FOXO3a was shown to be mono-ubiquitinated upon oxidative stress. The de-ubiquitinating enzyme USP7/HAUSP (herpesvirus-associated ubiquitin-specific protease) bind FOXO3a and FOXO4, leading to their de-ubiquitination and negative regulation of their transcriptional activity [94].

Transcriptional regulation by FOXO3a

FOXO transcription factors bind the DNA directly as monomers and activate gene expression by recruitment of the basal transcriptional machinery. This binding is mediated by helix-3 of their DNA binding domain to the major groove of DNA in similar fashion to other Forkhead family members such as FoxA1 [10]. The Forkhead responsive elements (FHRE) of FOXO transcription are only slightly variable from the general FHRE, so that Pan FHRE is G/aTAAAC/tAa and the optimal FOXO FHRE is GTAAACAA (TTGTTTAC) [28, 76]. This conservation of DNA recognition sites may explain the tissue specific activities of some Forkhead transcription factors and the overt phenotype of knockout mice so far generated.

FOXO3a has been shown to regulate a large array of genes governing diverse cellular processes such as cell cycle regulation (p21Cip1, p27Kip1, D-type Cyclins, Rb2/p130, Cyclin B1, Plk, Cdc2 and BTG1), cell death (BIM, TRADD, TRAIL and FasL), DNA repair (GADD45), stress responses (MnSOD and Catalase), tumourgenesis (TGFβ, IκB and BCL-6) [31, 36, 52, 63, 82, 86, 89].

Our understanding of FOXO3a dependent activation is still in its infancy as few reports highlight the molecular mechanisms involved [50, 51]. Upon cessation of growth factor or oncogenic signalling, PKB is dephosphorylated, effectively releasing FOXO3a transcription factor from the molecular chaperone 14-3-3 leading to its nuclear localisation and activation. Upon translocation to the nucleus, FOXO3a transcription factor binds HATs such as p300, CBP (CREB binding protein) and PCAF (p300/CBP-associated factor) that acetylate FOXO transcription factors [62, 66, 75]. The complex is then translocated to the target promoters, whereby FOXO3a binds DNA and leading to histone tail acetylation [93]. This acetylation of histone tails creates an open chromatin state allowing the loading of the basal transcriptional machinery to drive mRNA synthesis [65]. This is a model of gene activation by FOXO3a transcriptional activation, rather than an empirically evaluated mechanism. This is complicated by the fact that reversible acetylation of FOXO transcription has been reported to activate FOXO3a [14, 66], and repress their activity [25]. This discrepancy arises from studies of oxidative stress responses mediated by FOXO transcription factors. Emerging evidence suggests that FOXO3a, for instance, promotes the expression of genes differentially in high redox states (addition of hydrogen peroxide), as compared to mild conditions such as inhibition of PI3K [30].

FOXO3a dependent gene repression is yet to be investigated. Although, some evidence suggest that FOXO3a represses the expression of Cyclin Ds [82], the mechanism whether direct or indirect remains to be elucidated.

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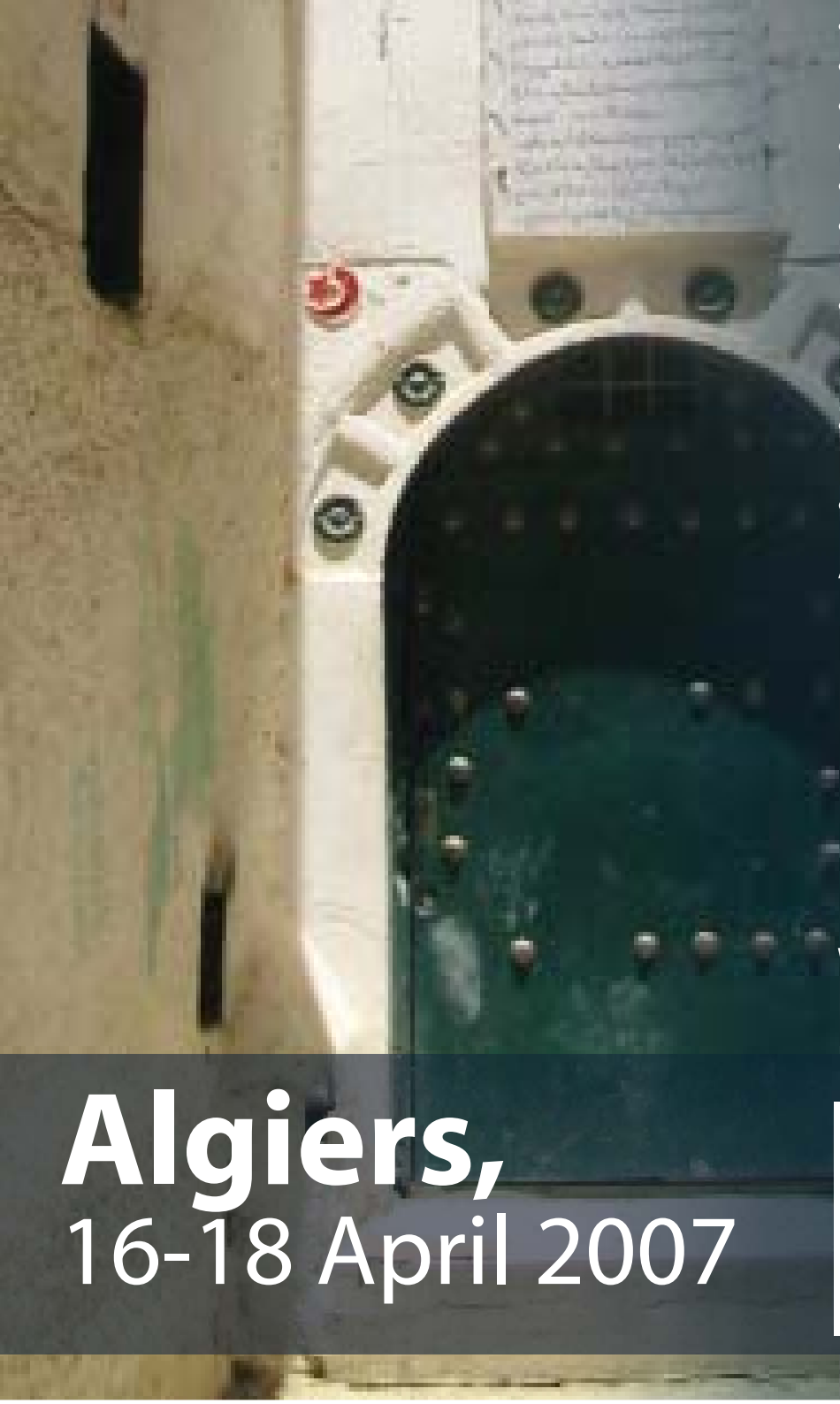

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SiGe strain tuning platforms: Material properties and advantages offered to the Si-based technology

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Abstract

Silicon\Silicon Germanium (Si\SiGe) heterostructures have gained a lot of interest in recent years due their ability to enhance current CMOS device performance such as carrier mobility as well as allowing new concepts to be explored like SiGe-based Quantum Cascade Lasers. In this article we examine the material and electronic properties of SiGe systems and the challenges facing the growth of high quality defect-free SiGe virtual substrates. The advantages of using relaxed SiGe virtual substrates and the importance of band structure and strain engineering, in enhancing the performance of CMOS technology, are outlined. Material and strain properties together with strain relaxation techniques are also discussed.

1. Introduction

The CMOS industry is one of the biggest electronic industries in the world; it is worth over $100 billion, with more than 98% of this belonging to the silicon based integrated circuit market [24]. The dominance of silicon can be attributed to several factors including the abundance of silicon raw material, the mature and cheap processing of silicon electronic devices and more importantly the readily formed oxide SiO2 which allowed Si to dominate over faster switching materials such as GaAs.

In order to increase the speed of silicon-based devices, as predicted by Moore's law, it is necessary to continually scale these devices down. However, fundamental limitationions such as tunnelling of electrons through the gate oxide, when it becomes too thin (less than 0.8nm), the drain induced barrier lowering (DIBL) [24] and the fabrication limits imposed using optical lithography, will soon hit the barrier of device integration. One solution to the above mentioned problems may be achieved through incorporating new materials, which are compatible with current CMOS fabrication processes, to enhance the device performance without the need to scaling it down. Germanium has been proven to be one such material.

Germanium is completely miscible in silicon and has the same diamond structure. Therefore, it is possible to form perfect Si_xGe_{1-x} alloys with any fraction $\boldsymbol{x}$. Germanium has a lattice constant 4.2% larger than silicon, so any normal, relaxed alloy of SiGe has a lattice parameter between those of silicon and germanium. When a thin layer of silicon is grown pseudomorphically on a relaxed SiGe alloy, the Si layer conforms to the larger lattice spacing of the SiGe template. This is done by expanding laterally and

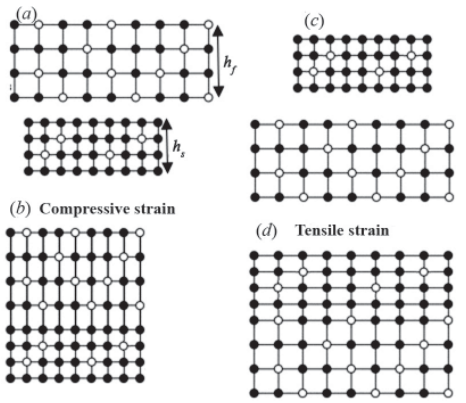


Figure 1:

A schematic diagram showing a $Si_{1-x}Ge_x$ film to be grown on $Si_{1-y}Ge_y$ substrate [(a): x > y, (c): x < y]. (b) A schematic diagram showing the tetragonal distortion of the top film from (a). (d) A schematic diagram showing the top film in (c) being tensile strained. (After [26]).

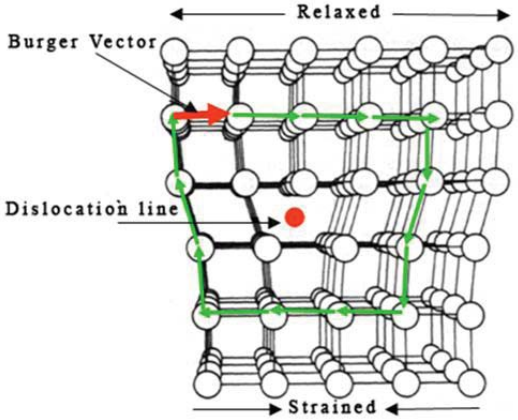


Figure 2:

Structure of an edge dislocation in a simple cubic crystal with a Burger vector perpendicular to the dislocation line (After [15]).

contracting vertically. This biaxial distortion of the Si lattice has profound consequences on the electronic band structure of Si and leads to enhanced electron and hole mobility [18], consequently increasing the drift velocity of electrons and hole in the device i.e. electron and hole mobility. This is known as straining Si; it induces splitting of the band structure and loss of degeneracy in both valence and conduction bands. It also reduces inter-valley and inter-band phonon scattering, hole effective mass due to band warping, and preferential thermal population of electron states with light effective mass [20]. The relaxed SiGe buffer layer is usually termed as *virtual substrate* and it needs to be of high quality or defect-free. The relaxation of SiGe occurs at the critical thickness, where misfit dislocations form at the interface to relieve the strain. Due to the detrimental effect on device performance, the density of threading dislocations must be kept low [9]. Many design methods and structures have been proposed to achieve high quality virtual substrates with low threading dislocation density; these include graded layer approach, terrace grading [21] and incorporation of carbon to control the strain in the SiGe layers. However no optimum design has been reported yet.

Strain tuning in the Si/SiGe layers can be achieved by controlling the percentage of Ge in the alloy, hence allowing the band gap engineering and the physics to be studied in different Si/SiGe systems. Band gap engineering together with controlling the lattice constant, by tuning the degree of strain in the Si/SiGe layers, allows virtual substrates to be lattice matched to the III-V materials [10]. Hence it is possible to grow III-V semiconductors alongside conventional Si-CMOS, permitting optoelectronic and CMOS devices to be fabricated in a single chip [1, 10].

The advantages of SiGe also extend to interesting applications in both optoelectronics and telecommunications. The poor efficiency of Si in providing laser action, due to its indirect band gap, has led to the consideration of a Si/SiGe Quantum Cascade Laser (QCL), which is currently driven by the success of III-V QCLs [3].

An indication for the possibility of achieving a Si/SiGe QCL is the intersubband electroluminescence from Si/SiGe heterostructures, which has been demonstrated in both the mid-infrared and the technologically important THz regions [25]. Results so far show that a Si/SiGe QCL can be realised [25] and will have considerable advantages over III-V QCLs. All Si/SiGe quantum cascade structures investigated to date rely on transitions in the valence band. This is mostly related to the heavy electron mass in the tunnelling direction of the conduction band [23], and the band discontinuity being mostly in the valence band. To achieve significant band discontinuity in the conduction band the growth of high quality relaxed SiGe virtual substrates, with high Ge concentration, is required [2, 19].

2. Strain, Dislocation and Critical Thickness

As stated earlier, germanium has a lattice constant 4.2% larger than silicon. When a relaxed $Si_{1-x}Ge_x$ is formed the lattice constant of the alloy is almost linear as predicted by Vergard's law [23] and is given by the following equation

$$a_{Si_{1-x}Ge_x} = 0.4531 + 0.0199x + 0.0002733x^2 \text{ (nm)} \quad (1)$$

If a film of $Si_{1-x}Ge_x$, with thickness h_f and lattice constant a_f, is grown on top of $Si_{1-x}Ge_y$ substrate of thickness h_s and lattice constant a_s, then the film is said to have a lattice mismatch with respect to the substrates represented by the misfit parameter [13]

$$\varepsilon_m = \frac{a_s - a_f}{a_f} \quad (2)$$

If $x < y$, then the film is compressively strained (Figure 1(b)), and for $x > y$ the film is said to be in tensile strained (Figure 1(d)).

If $h_f << h_s$, then the elastic mismatch is entirely accommodated in the film [13] and the elastic strain of the film is ε_m. In general, the equi-biaxial elastic strain in the film material ε_f, and in the substrate material are given by equation (3)[13].

$$\varepsilon_f = \varepsilon_m \frac{h_s G_s}{h_f G_f + h_s G_s}, \quad \varepsilon_s = -\varepsilon_m \frac{h_s G_s}{h_f G_f + h_s G_s} \quad (3)$$

where G_i are the shear moduli of the material at hand.

These elastic strains are in the plane of the film and the substrate ($\varepsilon_x = \varepsilon_y$), but they also induce a strain in the perpendicular direction

to the interface, resulting in a tetragonal distortion to the lattice (figure 1(b)). If the material is assumed isotropic, then the perpendicular strains are given by the following equation [13].

$$\varepsilon_f^{\perp} = -\frac{2\nu_f}{1-\nu_f}\varepsilon_f \,,\; \varepsilon_s^{\perp} = -\frac{2\nu_s}{1-\nu_s}\varepsilon_s \qquad (4)$$

where ν_i are the Poisson's ratios of the material.

It is this strain component that is commonly detected in an X-ray experiment of thin film deformation [13].

As the thickness of the deposited film increases, the strain energy ($\sim\varepsilon^2 h$) also increases; eventually it will cost too much energy to strain additional heterolayers in coherence with the substrates. Therefore a critical thickness h_c exists, at which the film starts to relax. Relaxation occurs by introducing defects or misfit dislocations which act to relieve the strain in the epitaxial film.

A dislocation is usually characterised by a Burger vector which is found by drawing a Burger circuit path around the dislocation line as shown in Figure 2.

The dislocations in the silicon germanium system occur at 60° with the Burger vector parallel to the [110] direction [13]. As well as relaxing the epitaxial layer, these dislocations interact with the electrical, thermal and optical properties of the material degrading its performance.

Misfit dislocations extend through the film by the gliding of a threading dislocation (TD), which connects the ends of the dislocation to the surface, as shown in figure 3. Threading dislocations can seriously degrade device performance; hence their density should be kept low.

The strain δ relieved by ρ_t threading dislocations per unit area is given by the following equation [11].

$$\delta = \frac{\rho_t b l}{4} \qquad (5)$$

Where l is the length travelled by the TD (i.e. the misfit segment in figure 3), b is the Burger's vector magnitude and the dislocations are assumed to be 60° dislocations. Equation (6) [12, 26] is an empirical formula for the dislocation velocity v under an effective stress σ_{eff}.

$$v = 9.8 \times 10^4 \left(\frac{v_{eff}}{v_0}\right)^2 \exp - \left(\frac{2.25 eV}{k_B T}\right) \qquad (6)$$

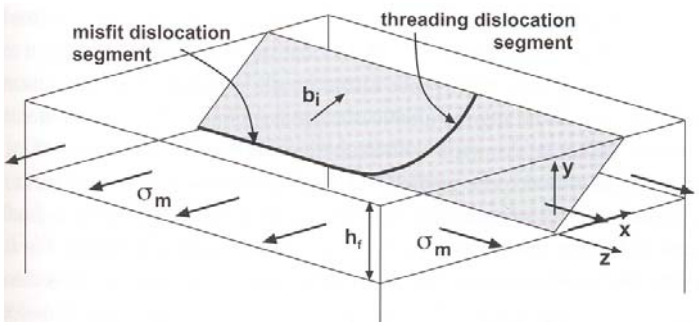


Figure 3:
A threading dislocation on a glide plane in a film of thickness subject to a uniform mismatch stress σ_m (After [13]).

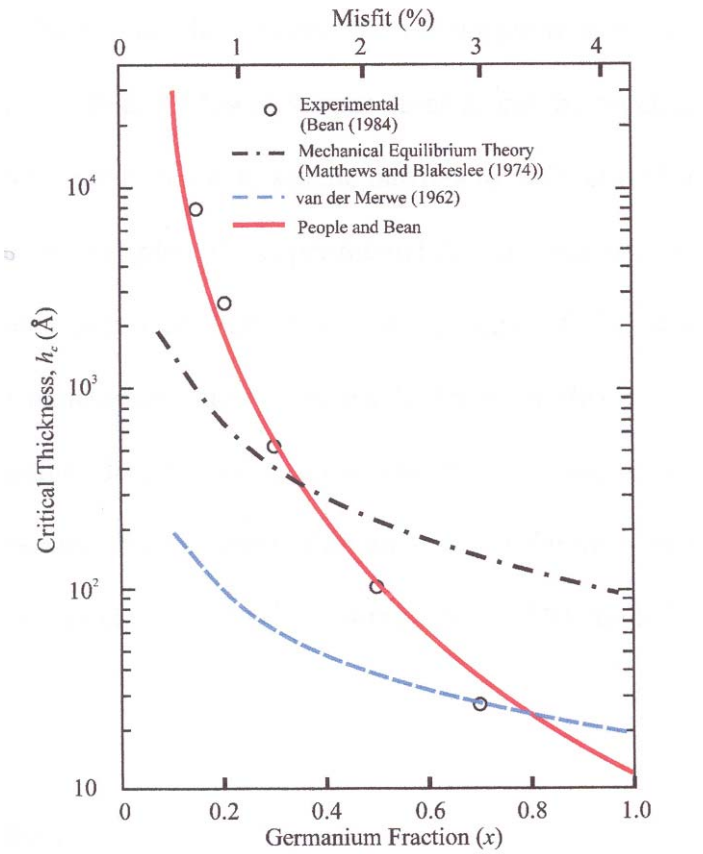


Figure 4:
The critical thickness as a function of Ge content and lattice misfit for a Si/$Si_{1-x}Ge_x$ /Si heterostructure (After [4]).

Here v is in mm/s, σ_{eff} and σ_0 are in MPa, σ_0 is usually taken to be 1MPa and the pre-multiplier constant in the above equation has the dimension of velocity. Hence the rate of strain relief is related to the TD velocity in the following way [11].

$$\frac{d\delta}{dt} = \frac{\rho_t b v}{2} \text{ where in this case } \frac{dl}{dt} = 2v \qquad (7)$$

It is important to note that the above equations describe the motion of the TD in steady state and that nucleation is not explicitly included [11]. These equations will also be important later to the design of relaxed virtual substrates.

Many models have been developed to predict the critical thickness h_c, mentioned earlier, beyond which the onset of misfit dislocations is favourable. The idea of the critical thickness was first discussed by Frank and Van der Merwe [4]. Van der Merwe used a thermodynamic model where the energy of a system is minimised by the formation of a periodic array of dislocations, this produced the following formula [25] for h_c.

$$h_c \simeq \frac{19}{16\pi^2}\left(\frac{1+\nu}{1-\nu}\right)\left(\frac{b}{\varepsilon_m}\right) \qquad (8)$$

Later Matthews and Blakeslee used a similar approach by balancing the forces acting on the dislocation. This produced a critical thickness of [25]:

$$h_c \simeq \frac{b}{2\pi\varepsilon_m}\left(\frac{(1-\nu)\cos^2\theta}{(1-\nu)\cos\lambda}\right)\left(\ln\left(\frac{h_c}{b}\right)+1\right) \quad (9)$$

where θ is the angle between the Burger's vector and the dislocation line and λ is the angle between the Burger vector and the direction in the interface normal to the dislocation line. Figure (4) shows the critical thickness as a function of Ge composition for a single $Si/Si_{1-x}Ge_x/Si$ heterostructure.

Experimentally it was observed that many pseudomorphic layers could be grown well above the critical thickness values predicted from the above models [23]. This has been partially related to the difficulty in detecting low densities of dislocations but is predominantly related to a kinetic barrier to the relaxation process allowing metastable layers to be grown.

3. Growth of SiGe Virtual Substrates

The growth of a relaxed $Si_{1-x}Ge_x$ buffer or substrate has many applications in both electronics and optoelectronics. These substrates are commonly termed "virtual substrates" because it is hard to form SiGe wafers from a $Si_{1-x}Ge_x$ melt due to the large separation of the liquidus and solidus lines in the $Si_{1-x}Ge_x$ phase diagram [16].

The main techniques used in growing $Si_{1-x}Ge_x$ virtual substrates are

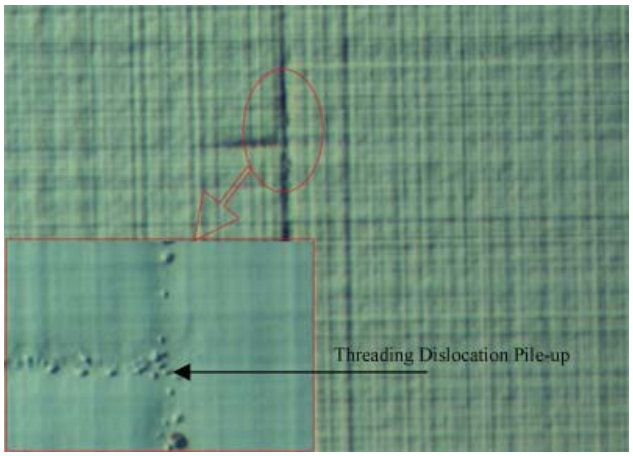


Figure 5:
An optical micrograph image of the surface of a $Si_{1-x}Ge_x$ virtual substrates graded to 30% Ge. Dislocation pile-up is shown by the black arrow.

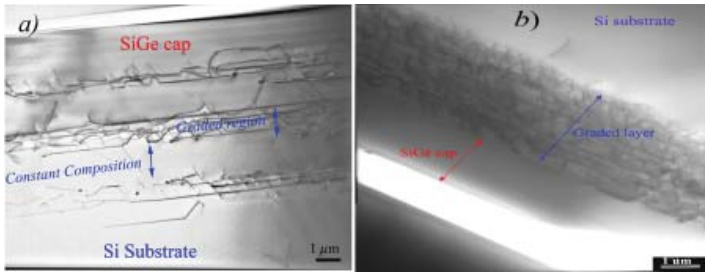


Figure 6:
a) Cross sectional TEM for the terrace graded virtual substrates. Dislocations are confined in the graded regions with some threading components penetrating the constant composition layers. b) XTEM for a linearly graded virtual substrate.

Molecular Beam Epitaxy (MBE) and Chemical Vapour Deposition (CVD). Although the first high quality $Si_{1-x}Ge_x$ virtual substrate was achieved using MBE [24], CVD is the dominant technique used by the semiconductor industry as a production tool. The dominance of CVD in the industry is mainly related to the particulate density. For high yield in CMOS and bipolar production using lithography techniques, the particulate density must be kept as close to zero as possible. However in MBE this is hard to achieve as the material is deposited on the walls of the growth chamber and over time it may fall off and create particles [23].

One obvious way to produce relaxed virtual substrates is to grow a thick layer of $Si_{1-x}Ge_x$ straight on top of a silicon wafer. Provided the thickness of the $Si_{1-x}Ge_x$ layer is well above the critical thickness then relaxation will occur. However this approach to virtual substrates produces a large number of misfit dislocations which interact and penetrate the epilayer resulting in large threading dislocation densities. This is detrimental to the quality of the virtual substrate. Typical threading dislocation densities using this approach are around $10^9 cm^{-2}$, which is far too large than that which can be tolerated by any electronic or optoelectronic device.

In order to reduce the density of threading dislocations a method must be found to increase the length of the misfit segments. In the ideal case these threading segments would travel to the edge of the wafer without a threading component penetrating the epitaxial layers. There are three conditions for achieving long misfit segments [23]:

a) High growth or anneal temperature to enable high gliding velocity of the misfit dislocation (Equation 6).

b) The interactions with other threading dislocation which result in pinning is required to be low.

c) The activation energy of misfit nucleation is required to be higher than that of dislocation glide.

One method to achieve the above criteria is to slowly grade the germanium composition from 0% up to the required Ge composition. This allows misfit dislocations to form in many different planes consequently reducing their interactions [21]. It was found that the optimum grading rate [11] is 10% Ge/μm for Ge content up to about 30%. Using lower grading rates and higher growth temperatures substantially improves the virtual substrates and leads to lower TD densities. However, low Ge grading rates result in thicker virtual substrates, and because the thermal conductivity is much lower in SiGe layers than in bulk silicon or bulk germanium layers [29], this leads to serious problems in a number of electronic and optoelectronic devices where heat dissipation is necessary. Thick virtual substrates also required long fabrication time hence increasing their cost.

Graded layers also suffer from a number of problems such as dislocation pile-ups; and inhomogeneous strain fields created by the buried misfit dislocations lead to surface crosshatch patterns [11] as shown in figure 5. Threading dislocations can be blocked by this crosshatch leading to the formation of pile-ups. Dislocation pile-ups can in turn arrest the motion of other dislocations distorting the surface of the virtual substrates even further.

Another method for growing high quality virtual substrates is by "terrace grading" the film [21]. In this method the linear grading of Ge is interrupted by uniform layers of constant germanium composition at regular intervals. This has the effect of reducing dislocation

pile-ups and improving the surface morphology as a consequence of spatially separating the graded layers. Figure 6 shows a cross sectional transmission electron microscope (XTEM) images of a linearly graded and a terrace graded virtual substrate; the network of threading dislocations is more complicated in the linearly graded substrate. Most virtual substrates are terminated with a thick constant composition cap layer to ensure relaxation as well as separating dislocations from any future devices grown on these virtual substrates.

Other techniques for virtual substrates include the use of silicon-on-insulator as a base substrate [27], low temperature Si buffer layer to release the stress and suppress threading dislocations [5] and recently the use hydrogen ion implantation [23]. The area of virtual substrate growth is still under heavy research and many techniques are still being developed to produce high quality SiGe virtual substrates with low threading dislocation density.

4. Electronic Properties of SiGe System

Both bulk silicon and bulk germanium are indirect band gap materials with band gap energy of 1.12 eV and 0.66 eV respectively at 300 K [8]. For pseudomorphic strained $Si_{1-x}Ge_x$ layers grown on (100) silicon, the band gap $\boldsymbol{E_g(x)}$ is still indirect and varies with the germanium composition according to the following equations [18].

$$\begin{aligned} \boldsymbol{E_g(x)} &= (1.155 - 0.43\boldsymbol{x} + 0.0206\boldsymbol{x}^2)\ \boldsymbol{eV} \quad \text{for} \quad 0 < \boldsymbol{x} < 0.85 \\ \boldsymbol{E_g(x)} &= (2.010 - 1.27\boldsymbol{x})\ \boldsymbol{eV} \quad \text{for} \quad 0.85 < \boldsymbol{x} < 1 \end{aligned} \tag{10}$$

The strain in the lattice alters the band structure of semiconductors by either shifting it in energy, removing degeneracy effect, distorting it, or indeed a combination of the three. Calculation of the band structure for different SiGe systems is complicated but has been performed, in many papers, using either pseudopotentials or $\boldsymbol{k \cdot p}$ theory. Calculation of the band structure allows the determination of effective masses and transport properties in SiGe heterostructures.

The six ellipsoidal energy shells shown in Figure 7(a), represent constant energy surfaces for the Si conduction band. Under biaxial compressive strain, the six-fold degeneracy in Si is split, the [001] conduction bands (two-fold degenerate Δ_2 bands) move up in energy, while the [100] and [010] conduction bands (four-fold degenerate Δ_4 bands) move down in energy, as shown in Figure 7(b). This splitting of degeneracy in the conduction band reduces the conductivity effective mass and suppresses intervalley scattering [22], therefore enhancing the transport properties.

Biaxial in-plane compression also splits the top of the valence band, with the light hole (LH) moving down in energy and the heavy hole (HH) being raised in energy (Figure 7(b)), thereby reducing both intersubband and intrasubband scattering [22]. In the case of tensile strained (pseudomorphic) Si, the direction of motion of the split levels, both in the conduction and valence bands, is reversed.

Excellent transport properties can be achieved using strained silicon grown on a relaxed SiGe virtual substrate. Figure 8 [5] shows electron and hole mobility enhancements as a function of Ge content in the underlying virtual substrates. At low Ge content, the electron mobility is enhanced by 80% in strained Si compared to bulk Si, however the hole Mobility enhancement is only around 60%. To boost hole mobility further, higher Ge content ($\boldsymbol{x} > 0.4$) in the virtual substrate is needed; but this would limit the usable Si thickness grown on top, as it has to be less than the critical thickness. One solution around this problem is to use a Dual Heterostructrue (DH) [7], in which a compressively trained SiGe channel is introduced into the structure to serve as a hole channel. This was demonstrated to have both high hole and electron mobility enhancement [14]. In such structures it is even possible for holes to have higher mobility enhancement than electrons, making it of great interest for CMOS applications.

The major advantage of Si/Ge heterostructures is the ability to grow structures with different energy band gaps (Equation 10) hence enabling both band gap and strain engineering on top of a silicon wafer. Conduction and valence band discontinuities in these structures al-

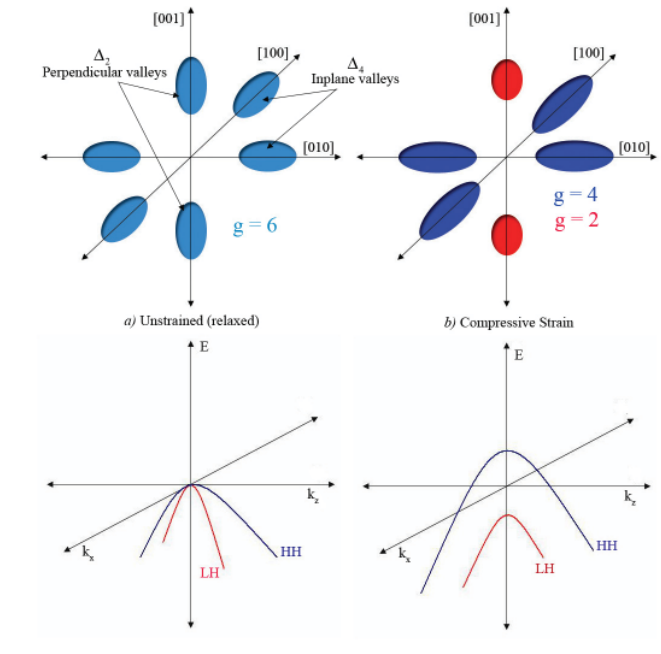
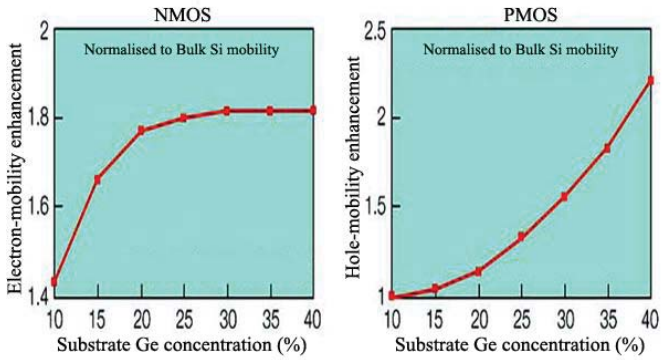


Figure 7 (left):
Illustrating the effect of compressive strain on Silicon conduction and valence bands. The six-fold degeneracy in the conduction band is split. The heavy hole band (HH) move up in energy and the light hole band (LH) move down in energy. The diagram is schematic only and not to scale (After [17]).

Figure 8 (below):
Electron and hole mobility enhancements in strained Si compared with bulk Si as a function of Ge content in the underlying SiGe buffer [7].



low systems to be designed where electrons and/or holes are confined in quantum wells or quantum mechanical barriers. This is particularly important for junction device applications. This technology has been successfully used to engineer many devices such as SiGe heterojunction bipolar transistor (HBT) and SiGe modulation-doped field effect transistor (MODFET) both of which have application in areas where low noise and high linearity is required [23]. Examples of devices that are still under research and development include SiGe Resonant Tunnelling Diodes (RTDs) and SiGe quantum cascade lasers.

5. Conclusion

There is a real possibility that SiGe will one day be used in every Si-based electronic and optoelectronic device; as an indication is the development of SiGe HBTs and the use of strained-Si in CMOS technology, which helped improve the performance Si based transistors. The mature and reduced cost Si technology may also help for the fast development of SiGe devices, hence moving from research to mass production for the market. However before this could happen SiGe strain tuning platforms or SiGe virtual substrates have to reach a high enough quality (in terms of defect density and thickness) to allow for mass production and the wide use in Si CMOS technology. A recent study [28] has shown that further improvement to the quality of SiGe virtual substrates can be still achieved using the terrace grading method. This can be done by optimising the growth temperature and in situ anneal. The same study revealed that the relaxation of the first terrace is critical and can help reduce the threading dislocation density in all subsequent layers dramatically. Thus it was emphasised that the relaxation of the first terrace should be achieved either by in situ anneal, or decreasing the grading rate of Ge, or indeed a combination of both. For the subsequent terraces it was found that annealing can be used to minimise the surface roughness of the SiGe virtual substrate.

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